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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,998	12/07/2000	Hilary A. Coller	2825.2006-001	3011

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 01/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/732,998	Applicant(s) COLLER ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 21-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/23/02, as Paper No 13. Claims 1-35 are pending in the application. Claims 1-12 and 21-35 and non-elected species have been withdrawn from consideration for the reasons set forth in the previous Office Action. Claims 13-20 (and the species EIF5A) are examined herein.

2. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

Response to Amendment

The amendment filed 10/23/02 has been entered. The objection to the specification because of an embedded hyperlink has withdrawn as the hyperlink has been removed.

Drawings

3. The corrected or substitute drawings were received on 10/23/02. These drawings are acceptable.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 13, 14, 15, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eilers et al. (EMBO J. Vol. 10, No. 1, pp. 133-141; 1991) in view of Adnane et al. (Oncogene, 1995; 10:381-387).

Eilers teaches a method for identifying MYC target genes (i.e. genes that are directly regulated by MYC transcriptional activity), said method comprising the steps of:

a) obtaining an indicator cell that expresses a chimeric receptor comprising MYC and a ligand binding domain (here, a Rat1a cell expressing a MYC-Estrogen Receptor (MYC-ER) chimera, see p. 133, second column and p. 138, Figure 6);

b) contacting the said indicator cell with an appropriate ligand (here, contacting the cell with estrogen, see p. 135, Figures 2 and 3) resulting in expression of MYC-activated genes (e.g. see p. 135, Figure 2), which can be evaluated by isolating the mRNA from the indicator cells and determining the level of gene expression by Northern blot analysis (see p. 135, Figure 2).

Eilers teaches that cyclohexamide can be added to the reaction in order to inhibit protein synthesis, which ensures that any modulation of gene expression is due directly to the effects of MYC and not a mediating protein (see p. 137, second column).

Eilers does not specifically indicate that the method can be used to identify agents which modulate (activate or inhibit) the transcriptional activity of MYC.

However, Adnane teaches a method of testing the ability of an agent to modulate the transcriptional activity of MYC. In general, the method encompasses expressing MYC and the agent of interest in a cell and evaluating the effect of the agent on the ability of MYC to activate a reporter construct. Specifically, Adnane teaches expressing MYC as a GAL4-MYC chimeric molecule in a cell transfected with a GAL4-dependent reporter vector alone or in a cell transfected with a GAL4-dependent reporter and a vector which expresses the test agent, Retinoblastoma (Rb). The results (see Figure 1b, p. 382) show that the relative expression of the

reporter gene (CAT) was increased 6.5 fold in cells transfected with all three constructs (GAL4-MYC, Rb, reporter), indicating the Rb activates the transcriptional activity of MYC. Furthermore, a relative expression level below 0 would indicate the agent molecule inhibits the transcriptional activity of MYC.

Eilers teaches a method a workable method to evaluate MYC transcriptional activity. The only element of the claimed method that Eilers does not teach is to add a test agent that is a candidate modulator of MYC transcriptional activity. Adnane indicates that a candidate agent can be tested for modulation of MYC transcriptional activity using a system comprising a MYC fusion protein and a reporter construct that indicates MYC transcriptional activity. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to create a method for identifying an agent that modulates MYC transcriptional activity by modifying the method of Eilers such that a second indicator cell is transfected with the MYC-ER expression vector and a vector expressing the agent of interest (RB, or any other agent of interest) with a reasonable expectation of success. The effect of the agent on MYC transcriptional activity could then be determined by comparing Northern blots of the first (MYC alone) and second (MYC+agent) indicator cells.

One of ordinary skill in the art would have been motivated to create the new method of identifying agents which modulate MYC transcriptional activity because the method of Eilers does not use an artificial reporter construct to indicate MYC transcriptional activity, but rather indicates MYC transcriptional activity by assaying actual genes that are directly regulated by MYC, thus making the new method an improved system for testing regulators of MYC transcriptional activity.

6. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eilers et al. (EMBO J. Vol. 10, No. 1, pp. 133-141; 1991) in view of Adnane et al. (Oncogene, 1995; 10:381-387), and further in view of Lee et al. (PNAS Vol. 94, pp. 12886-12891; 1997).

Eilers teaches a method for identifying MYC target genes (i.e. genes that are directly regulated by MYC transcriptional activity), as mentioned above.

Eilers does not specifically indicate that the method can be used to identify agents which modulate (activate or inhibit) the transcriptional activity of MYC.

Furthermore, Eilers does not teach that the 4-hydroxytamoxifen can be used a ligand to induce the chimeric MYC molecule.

Adnane teaches a method of testing the ability of an agent to modulate the transcriptional activity of MYC comprising expressing MYC and the agent of interest in a cell and evaluating the effect of the agent on the ability of MYC to activate a reporter construct (as mentioned above), but does not teach that 4-hydroxytamoxifen can be used in the method.

Lee teaches a method for identifying genes regulated by MYC that is very similar to the method of Eilers. However, the method of Lee comprises the use of a chimeric receptor (ΔMYC-ER) comprising MYC fused to a modified ER-ligand binding domain. The ligand 4-hydroxytamoxifen (4-OHT) binds to and activates the chimeric ΔMYC-ER molecule resulting in modulation of transcription of MYC-regulated genes, such as repressed expression of gas1 (e.g., see p. 12890, Figure 4).

Lee indicates that the ΔMYC-ER chimeric molecule, "[E]mploys a mutant of the hormone binding domain that selectively binds 4-OHT, a synthetic analog of 17-beta-estradiol, but not 17-beta-estradiol itself, which is present in serum, thus facilitating the culture of these

cells during the experiment. In addition the mutation in the ER hormone binding domain abolishes the inherent ligand-dependent transactivation activity of the ER, thereby permitting study of transcriptional control by exogenous domains in hormone binding domain fusion proteins." (see p. 12889, first column).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to create a method for identifying an agent that modulates MYC transcriptional activity by combining the teachings of Eilers and Adnane, as mentioned above; and to further modify the MYC-ER chimeric molecule so that it comprised a modified ligand binding domain that specifically binds 4-hydroxytamoxifen.

One of ordinary skill in the art would have been motivated to make the modifications taught by Lee because Lee indicates that the ΔMYC-ER chimeric molecule would be an improvement over the MYC-ER chimeric molecule (used by Eilers) as the modified chimeric ΔMYC-ER would not be responsive to 17-beta-estradiol present in culture serum, and would be unaffected by inherent ligand-dependent transactivation activity of the ER.

7. Claims 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eilers et al. (EMBO J. Vol. 10, No. 1, pp. 133-141; 1991) in view of Adnane et al. (Oncogene, 1995; 10:381-387) and further in view of Zhu et al. (PNAS Vol. 95, pp. 14470-14475; Nov. 1998).

Eilers teaches a method for identifying MYC target genes that are directly regulated by MYC transcriptional activity using a MYC-ER chimeric molecule sensitive to estrogen (as mentioned above).

Adnane teaches a method of testing the ability of an agent to modulate the transcriptional activity of MYC comprising expressing MYC and the agent of interest in a cell and evaluating the effect of the agent on the ability of MYC to activate a reporter construct (as mentioned above).

However, neither Eilers nor Adnane teach that the level of gene expression can be determined by hybridization to an oligonucleotide microarray. Additionally, neither Eilers nor Adnane teach that the gene whose level of expression is being monitored is EIF5A, or that the level of gene expression is determined by hybridization to an oligonucleotide microarray.

Zhu teaches that gene expression in cells can be monitored using an oligonucleotide microarray, and specifically teaches that EIF5A gene expression can be monitored by hybridization to the oligonucleotide microarray (seep. 14470, under "Sample Preparation and Analysis with DNA Arrays"; and p. 14472, second column, Table 1 under "Translation factors").

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of invention to modify the method suggested by Eilers and Adnane above with the assay of Zhu to create a method that utilizes a cell expressing a MYC-ER chimera and estrogen to enhance/inhibit MYC-dependent transcriptional regulation of gene expression, and to assay the resulting effect on gene expression using a microarray, wherein the gene whose level of expression is being evaluated for regulation is EIF5A.

The motivation to combine the teachings of Eilers with Zhu is evidenced by the Eilers' teaching that transcriptional gene regulation can be monitored by evaluating the mRNA levels (e.g., see, p. 135, Figure 2), and Zhu's teaching that, "DNA array assay is performed easily and can detect subtle changes in mRNA levels" (see p. 14470, first column). Furthermore, Zhu teaches an oligonucleotide microarray that useful for monitoring the expression level of EIF5a (see p. 14472, second column, Table 1 under "Translation factors"). Therefore evaluating gene expression using the oligonucleotide microarray taught by Zhu would necessarily evaluate the level of EIF5A gene expression.

Response to Arguments

8. Applicant's arguments with respect to the rejection of claims have been fully considered. It is acknowledged that the references did not specifically teach all of the limitations of the claims. Therefore, the previous rejections have been withdrawn. However, new grounds of rejection have been applied.

Conclusion

No claim is allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
December 29, 2002

DAVE T. NGUYEN
PRIMARY EXAMINER